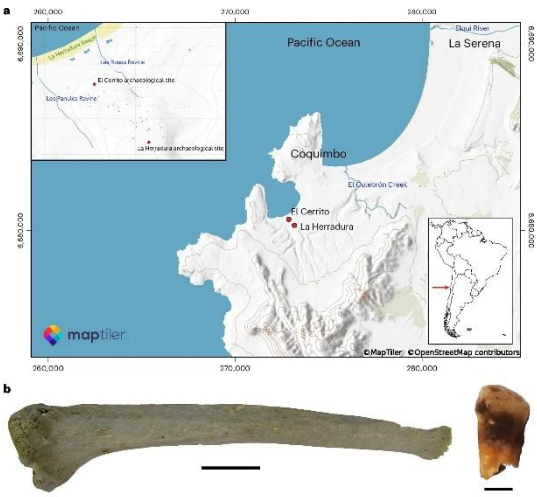
In South America Back 4,000 Years Scientists Trace Leprosy's Roots

Researchers analyzed Mycobacterium lepromatosis genomes from 4,000-year-old human remains, revealing a long history of leprosy in the Americas.

Leprosy (also known as Hansen's disease) is caused by Mycobacterium leprae and M. lepromatosis. M. lepromatosis has been regarded as the second causal pathogen for Hansen's disease and is associated with more severe forms of the disease, including Lucio's phenomenon and diffuse lepromatous leprosy. Untreated individuals can develop chronic peripheral neuropathy and physical impairment. Many infected subjects remain asymptomatic, impeding diagnostic and control measures.

Ancient M. leprae genome analyses support its infectious potential spanning millennia. Humans are the primary host of Hansen's disease, but maintenance of the causal bacteria in animals raises concerns about their potential as zoonotic reservoirs. Nine-banded armadillos are known M. leprae sources, while red squirrels can harbor both M. lepromatosis and M. leprae. The recent detection of M. leprae in archeological rodent bone suggests cross-species infectivity in historical periods.

Understanding of the evolutionary history and distribution of M. lepromatosis is limited, as only a few cases of infection have been molecularly confirmed. Studies suggest its presence in Southeast Asia and the Americas. Analyses involving ancient and modern genomic data consistently support the origin of M. leprae outside the Americas. However, the detection of M. lepromatosis has not been reported in archeological contexts.



Study and Results

In the present study, researchers analyzed M. lepromatosis genomes from 4,000-year-old human skeletal remains from distinct archeological contexts. First, 19 bones and 35 teeth with pathological lesions suggestive of infection, belonging to 41 individuals, were sampled from five archaeological sites in Chile.

The paper notes that while the bone changes in the two infected individuals were consistent with Hansen's disease, they were not definitively diagnostic on their own, underscoring the importance of molecular analysis for confirmation. A small quantity of each tissue was extracted, and a DNA library was constructed for sequencing.

Data were screened for various pathogenic viruses and bacteria following a hypothesis-free method. This revealed several thousand DNA fragments with homology to M. lepromatosis in two archeological tissues, a tooth from a male subject referred to as ECR003 at the El Cerrito site and a tibia from another male (ECR001) at the La Herradura site. Radiocarbon dating of these two elements indicated they were contemporaneous from 3,900 to 4,100 years ago.

DNA libraries were enriched using a probe set designed from a modern M. leprae reference panel, a methodological detail that resulted in some uneven coverage but still yielded exceptionally high-quality ancient genomes. These libraries were then sequenced to explore the suitability of genomic reconstruction. Various mycobacterial species were distinguished using a competitive mapping approach. The mean genomic coverage was 74-fold for ECR003 and 45-fold for ECR001 when mapped against a modern M. lepromatosis genome reference isolated from a Mexican patient.

Further, the researchers investigated divergence between M. leprae and M. lepromatosis given the genomic decay and reduction in M. leprae over evolutionary timescales. To this end, a pangenomic analysis revealed a high level of divergence, with about half of the protein-coding regions showing at least 50% sequence homology between the two pathogens. A mapping-based approach showed that the two pathogens shared only ~25% nucleotide identity.

Next, the relationship between M. lepromatosis and other mycobacterial pathogens was investigated by analyzing the 16S ribosomal RNA locus. This indicated that M. leprae is the closest relative, despite their extensive divergence.

Further, a conservative genome-level phylogenetic reconstruction was performed, focusing on the diversity within M. lepromatosis, and was limited to the two ancient genomes, four modern human genomes, and six modern red squirrel genomes.

There was a robust and distinct separation between rodent- and human-associated lineages, where the ancient genomes formed a sister clade to the cluster of all human M. lepromatosis sequences.

The study's comparative analysis also called into question a previously reported M. lepromatosis genome from India, suggesting through competitive mapping that it showed far greater homology to M. leprae.

Furthermore, time-calibrated phylogenetic trees were generated using the radiocarbon ages of ECR001 and ECR003 skeletal elements, along with the collection year of all modern genomes, to estimate evolutionary rates and divergence times.

The evolutionary rate was estimated at 6.91 x 10-9 substitutions per site per year for M. lepromatosis, aligning with estimates for M. leprae. The median time for the most recent common ancestor (tMRCA) of M. lepromatosis was estimated to be approximately 26,800 years ago; however, the authors note that the small number of available genomes results in a wide potential date range of 4,206 to 115,340 years ago.

The divergence time for genomes from human hosts was estimated to be around 12,600 years (with a range of 5,304 to 49,659 years ago), while the tMRCA for the red squirrel clade was a much more recent 440 years.

Conclusion

Taken together, the study reveals a distinct evolutionary history for M. lepromatosis. This deep timeline, potentially stretching back to the Pleistocene-Holocene transition, contrasts sharply with other major pathogens, such as M. leprae and Yersinia pestis (the plague bacterium), which are thought to have emerged more recently in the Neolithic era with the rise of agriculture.

The fact that M. lepromatosis infections occurred in South America before the periods of known contact with European or Oceanian populations implies pathogen movement within human groups during an early peopling event or endemicity in the continent in a different reservoir species. The latter suggests that its current distribution originates from a post-colonial dissemination, making it one of the few diseases known to have emerged in the Americas.

The paper frames these findings within a 'One Health' perspective, calling for broader surveillance of animal reservoirs to better understand the disease's ecology and zoonotic potential.

Source:

https://www.news-medical.net/news/20250701/Scientists-trace-leprosye28099s-roots-in-South-America-back-4000-years.aspx